Neuropharmacology Summary

Opioids

Opioids work on a family of neurotransmitter receptors, the mu, delta, and kappa opioid receptors (MOR, DOR & KOR). The endogenous ligands for these receptors are a family of neuropeptides, the endomorphins (1&2, gene unknown) (MOR preferring), the enkephalins (met & leu, from the preproenkephalin gene) (DOR preferring), B-endorphin (from the proopioidmelanocortin or POMC gene) (MOR preferring), and the dynorphins (from the preprodynorphin gene) (KOR preferring). These receptors are found on neurons throughout the central and peripheral nervous systems, as well as on some immune cells. These receptors are found predominantly in neural systems involved in stress response, pain, motivation and reward. The receptors are inhibitory neuromodulators, their typical action is to reduce the likelihood of signal transmission through the neurons on which they are expressed.

The addictive propensity of opioids is likely due to their direct actions in the nucleus accumbens where they disinhibit the release of dopamine. Opioid effects may be reversed or prevented by administration of general opioid receptor antagonists such as naloxone or naltrexone.

Other major effects:
Analgesia is produced by selectively interupting the transmission of potential injury signals through a distributed network including primary sensory neurons, the spinal cord dorsal horn, the rostroventral medulla, the amygdala and insular cortex. *Respiratory Depression* is caused by direct action of opiate agonists on respiratory centers in the brain stem. *Constipation* is produced via a direct action on opioid receptors on the neurons which innervate the gut. *Miosis* is produced by an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. *Cough suppression* is mediated through direct action on receptors in the cough center of the medulla. Cough suppression can be achieved at lower doses than those required to produce analgesia.

Tolerance to opioid effects develops rapidly (unless opioid administration is matched to pain states). Cessation of opioid use following chronic use results in a severe abstinence syndrome. Symptoms of withdrawal include nausea and diarrhea, coughing, lacrimation, yawning, sneezing, rhinorrhea, profuse sweating, twitching muscles, abdominal and muscle pain/cramps, hot and cold flashes, piloerection and dysphoria. Elevations in body temperature, respiratory rate, heart rate, and blood pressure may also occur. The severity and duration of withdrawal symptoms are related to the rate of onset and clearance of the opioid.

Cocaine

Cocaine acts on monoamine transporters to block the reuptake of dopamine, norepinephrine and serotonin from synapses following their release. This will acutely increase activity at dopamine, adrenergic and serotonin receptors. Cocaine's major effects are thought to be due to actions on dopaminergic systems. Increased levels of extracellular dopamine in the nucleus accumbens are likely responsible for its addictive and motivational effects. Cocaine will also increase motor activity by increasing dopamine in the striatum, and at high doses can cause psychosis. Cocaine also acts as a sympathomimetic, increasing activity of the sympathetic nervous system, due to its action on norepinephrine transport.

Cannabinoids

Cannabinoids act upon a family of cannabinoid receptors, the CB-1 receptor found in the central nervous system, and the CB-2 receptor, found in the peripheral nervous system. Plant derived cannabinoids, such as delta-9 tetrahydrocannabinol, mimic the action of anandamide and 2-arachidonoylglycerol (2-AG) and other related polyunsaturated fatty acid derivatives, the endogenous CB receptor ligands. These endogenous transmitters are unique in that they are lipids

and thus may pass through cellular membranes. It is unclear if the release of endogenous cannabinoids is regulated, or if they simply diffuse away as they are produced.

Acutely, cannabinoids may produce dizziness, increased heart rate, red eyes, dry mouth, nausea, vomiting, drowsiness, increased appetite, altered mood, euphoria, decreased concentration, introspection, rapid thoughts, impairment of judgement, blurred vision, heightened sensory perception, hallucination, and perceptual distortion.

Cannabinoids are similarly addictive to alcohol. Animals will self-administer cannabinoids only under certain dosing schedules, and in some studies they have been found to be aversive. Both tolerance and dependence to cannabiniods do occur. Cannabinoid withdrawal symptoms include irritability, strange dreams, craving and aggression. Loss of appetite is also likely.

Barbiturates

Barbiturates act upon the GABA A receptor, an inhibitory neurotransmitter receptor that is activated by the amino acid GABA to open a chloride channel. Barbiturates are not agonists at the receptor, but rather modulators. They decrease the probability that the receptor enters a desensitized state, leading to burst-like activity at the channel. The net effect of this is to increase the inhibition of neuron firing produced via the GABA A receptor.

The addictive potential of barbiturates is thought to result from their disinhibition of norephinephrine containing neurons of the locus cerruleus (LC). Increased firing in LC neurons projecting to the nucleus accumbens, increases activity in this brain region thus reinforcing barbiturate administration.

Benzodiazepines

Benzodiazepines also act as modulators of the GABA A receptor. These compounds act on a single subunit of the GABA A receptor to increase the chloride ion conductance through the receptor when it is open. This again, results in increased GABAergic inhibition in cells expressing GABA A receptors that include this subunit. These compounds are thought to mimic the actions of certain steroid hormones, produced during the metabolism of progesterone and cortisol. These effects are thought to be responsible for the anesthetic effects of progesterone, and the fatigue associated with PMS and stress. Withdrawal from chronic benzodiazepine use results in a severe abstinance syndrome (similar to PMS), which includes increase propensity for seizure, anxiety, irritability, nervousness, and insomnia. Abdominal cramps, confusion, depression, perceptual disturbances, sweating, nausea, vomiting, parasthesias, photophobia, hyperacusis, tachycardia, and trembling also occur during benzodiazepine withdrawal, but the incidence is less frequent.

As with barbiturates, benzodiazepines are thought to be habit-forming due to their disinhibition of locus cerruleus neurons.

Amphetamines

Amphetamines act to reverse dopamine and NE transporteres, thus dumping dopamine and NE into dopaminergic and adrenergic synapses. They are thus sympathomimetics, mimicking the action of norepinephrine at on the sympathetic nervous system. Like cocaine and heroin, amphetamines increase dopamine concentration in the nucleus accumbens, likely accounting for their highly addictive nature.

There is evidence that chronic use of amphetamines can cause die back of dopaminergic synaptic terminals, leading to a Parkinson's like movement disorder.

Ketamine, PCP, and dextromethorphan

Ketamine, PCP, and dextromethorphan inhibit the activation of the NMDA receptor, an excitatory neurotransmitter receptor that is activated by the amino acid glutamate only when the neuron is simultaneously depolarized. Use of these NMDA receptor antagonists produces variable dissociative, hallucinogenic, and mood effects and sedation. They can produce symptoms similar to those of schizophrenia and have amnestic properties. Ketamine and PCP were developed and used as veterinary anesthetics. Dextromethorphan is used at low doses for cough suppression.

Ketamine, PCP and dextromethorphan can be addictive and induce drug seeking, however, many users dislike and avoid the drug's effects. They are not highly addictive. NMDA antagonists may cause memory, hormonal and mood disturbances.

LSD

Lysergic acid diethylamide acts as an agonist at 5-HT 2C receptors. It mimics the actions of serotonin at this subtype of serotonin receptor to produce changes in mood, hallucinations and dissociative effects. LSD is not generally addictive; it does not elicit drug-seeking behavior. However, regular users do develop tolerance to LSD's effects. LSD produces no physical dependence, and there is no known withdrawal syndrome.

Psilocybin (mushrooms) and mescaline are thought to work via similar mechanisms.

Ecstacy

MDMA, 3,4-methylenedioxymethamphetamine, is an amphetamine analog that probably has mixed actions. Like amphetamine is seems to have action on adrenergic and potentially dopamine receptors. Additionally, there is evidence that it acts upon 5-HT1A receptors. These seratonergic actions are apt to be responsible for the hallucinogenic, dissociative, and mood altering aspects of ecstacy's effects.

Ecstacy use has been associated with loss and restructuring of serotonergic synapses in experimental animals, similar to the neurodegeneration seen in long-term amphetamine abuse with a greater focus on serotonergic systems. Use of MDMA has been associated with increased incidence of learning and memory problems, depression and mood disorders in humans.

Ethanol

Ethanol has mixed actions with effects on various neurotransmitter systems at different doses. Ethanol is thought to have effects on the GABA A receptor, the adenosine transporter, and the NMDA receptor. Additionally, ethanol produces vestibular disturbances, dizziness and nausea, by altering the specific gravity of the fluid in the semi-circular canals. Ethanol is thought to increase GABA A receptor activity, thus increasing inhibitory neurotransmission throughout the nervous system. It is thought to block the adenosine transporter, thus increasing the activity of adenosine at adenosine receptors. As adenosine is thought to be important for inducing sleep, this activity is thought to be responsible for producing the drowsiness induced by ethanol. At very high concentrations, ethanol is thought to decouple the NMDA receptor from its calcium channel. This is thought to result in a loss of memory and eventually unconciousness.

Withdrawal from long term chronic ethanol use can result in a serious abstinence syndrome including tremulousness, anxiety, sinus tachycardia, and hypertension in the first 24 hours, followed by hallucinations, seizures, autonomic hyperactivity, and global confusion.

Caffeine

Caffeine produces its effects by antagonizing adenosine receptors. As mentioned before adenosine is thought to be involved in promoting sleep and producing drowsiness. Thus, caffeine acts as a CNS stimulant and has been shown to improve mental but not physical performance and

offset mental fatigue. Additionally, it acts as a diuretic and relaxes smooth muscle. Because of the latter effects is has been useful for treating bronchial asthma.

Caffeine does produce dependence and cessation of chronic use of caffeine results in a withdrawal syndrome with symptoms that include lethargy, anxiety, dizziness, and headache. Tolerance to caffeine's effects does appear to occur. Caffeine' addictive properties have not been properly examined, and there is debate in regards to its addictive potential. It does not appear to release dopamine in the nucleus accumbens however, it at some doses it does increase dopamine levels in the prefrontal cortex. Caffeine has been shown to be moderately reinforcing in animal studies but only with specific dosing and administration schedules.

Nicotine

Nicotine acts upon nicotinic acetylcholine receptors to produce its effects. These receptors are found in the CNS where they are deeply involved in selective attention and memory formation. Thus, nicotine has been shown to increase attention, cognitive performance and psychomotor activity, combat depression, alleviate anxiety, and produce euphoria. Additional actions within the limbic system result in fluid retention (promotes ADH release from the hypothalamus) and appetite suppression (probably due to release of 5-HT). Actions in the brainstem produce nausea and vomiting, however users develop rapid tolerance to these effects. Nicotine also has profound effects on the autonomic nervous system including increased heart rate and blood pressure from release of NE at the SNS and epinephrine from the adrenal. It is also an agonist at nAch receptors at the neuromuscular junction and at high doses can produce tremor and muscular paralysis.

Little tolerance to nicotine's effects develops, however extreme dependence and withdrawal are common. Cessation of chronic nicotine use result in a serious withdrawal syndrome including tingling in the hands and feet, sweating, intestinal disorders, and headache. Emotional and mental responses to withdrawal are also common and include insomnia, mental confusion, vagueness, irritability and depression. Nicotine is extremely addictive, and strongly releases dopamine throughout the reward pathway, as a result of agonism of nAch receptors in the ventral tegmental area and nucleus accumbens. Like other strongly addictive substances, users have serious nicotine cravings that may be cue associated and may persist long after the user has been abstinent and withdrawal symptoms have subsided.